

**Volume 9 of  
THE SCIENCE AND PRACTICE OF CLINICAL MEDICINE**

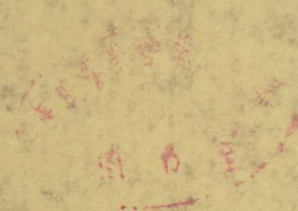
**John M. Dietschy, M.D.**

**Clinical Endocrinology  
and Metabolism**

**Principles and Practice**

**David Rabin, M.D.,  
F.R.C.P.**

**T. Joseph McKenna,  
M.D., F.R.C.P.I.**



# Clinical Endocrinology and Metabolism

## Principles and Practice

**David Rabin, M.D.,  
F.R.C.P.**

*Professor of Medicine  
Professor of Obstetrics and Gynecology  
Director of The Section of Endocrinology  
Vanderbilt School of Medicine  
Nashville, Tennessee*

**T. Joseph McKenna,  
M.D., F.R.C.P.I.**

*Director of The Department of Endocrinology  
St. Vincent's Hospital  
Dublin, Ireland*



**GRUNE & STRATTON**

*A Subsidiary of Harcourt Brace Jovanovich, Publishers*

**New York London**

**Paris San Diego San Francisco São Paulo  
Sydney Tokyo Toronto**



**Library of Congress Cataloging in Publication Data**

Rabin, David.

Clinical endocrinology and metabolism.

(The Science and practice of clinical medicine ;  
v. 9)

Includes bibliographical references and index.

1. Clinical endocrinology. 2. Metabolism—Disorders.

I. McKenna, T. Joseph. II. Title. III. Series.

[DNLM: 1. Endocrine diseases. 2. Metabolic diseases.

WK 100 R116c]

RC648.R33 616.4 82-2949

ISBN 0-8089-1394-8 AACR2

© 1982 by Grune & Stratton, Inc.

All rights reserved. No part of this publication  
may be reproduced or transmitted in any form or  
by any means, electronic or mechanical, including  
photocopy, recording, or any information storage  
and retrieval system, without permission in  
writing from the publisher.

*Grune & Stratton, Inc.*

*111 Fifth Avenue*

*New York, New York 10003*

Distributed in the United Kingdom by

*Academic Press Inc. (London) Ltd.*

*24/28 Oval Road, London NW 1*

Library of Congress Catalog Number

International Standard Book Number 0-8089-1394-8

Printed in the United States of America

## Foreword

There have been few more fruitful unions than that which has developed during the present century between basic science and clinical practice in the area of endocrinology. It has been said that some hormones are essential for life and that others make life worth living. Since hormones directly or indirectly affect every cell in the mammalian body, it is essential that every serious biologist and every physician should have a clear understanding of the nature of hormones, their effects, their mechanisms of action, and the normal and abnormal regulation of their secretion in health and disease.

In science, there are classical books that represent the best that is known at a particular time, setting it forth with memorable clarity and sound perspective. The book you are about to read is such a work. There are also books that are classical in the sense that they set forth for the first time seminal new concepts that are destined to influence the course of history. Sections of the book you hold are classical in this latter sense. But, in science, there can be no books that are definitive in the sense that they reveal all that is to be known about a subject, for science is a fabric woven of

concepts that are forever undergoing modification and elaboration, requiring continual reweaving of the fabric. To use the words of Robert Browning, in science it can always be said, "The best is yet to be."

The current textbook has been written by two endocrinologists whose paths crossed at Vanderbilt University during the 1970s, at a time when they both were attaining the peaks of their academic capabilities after having worked in widely separate parts of the world.

The excellence of this textbook is a reflection of the broad and deep experience the authors have had in endocrinology. Both are well-grounded in basic science and both are superb clinicians. They know endocrinology well, in all of its aspects, from personal experience. Equally basic to the excellence of this textbook is the fact that both writers are superb teachers, who write living prose, embodying a combination of detailed knowledge, clarity, well-placed emphasis, and style that will make this book an unforgettable part of the education of every reader.

Grant W. Liddle, M.D.

David Robin, M.D.  
Joseph McKenna, M.D.

Eagar Howard and Kenneth Hopkins Medical Center, Baltimore, Maryland; of University College, Dublin; the late Larry Kyle of Georgetown University Medical Center, Washington, D.C.; and Grant W. Liddle of Vanderbilt School of Medicine, Nashville, Tennessee, who brought us together for happy and productive years in the Division of Endocrinology. We are indebted to our colleagues, postdoctoral fellows, medical house



## Preface

The philosophy of the clinical practice of endocrinology and metabolism described in this text has evolved from our experience in day-to-day patient management. The material provides a thorough working knowledge of the physiology of the endocrine system, the basis from which familiarity with disease pathogenesis and symptomatology evolve. We emphasize practical clinical problems, examine the relative merits of available diagnostic procedures, and provide guidance for the most appropriate applications of various therapeutic options. Our goal is to provide a unified approach to endocrinology and metabolism with sufficient basic science and clinical awareness. We hope that the principles of clinical practice enunciated here will facilitate and enrich the reader's knowledge and understanding of the management of endocrine and metabolic disorders.

We acknowledge our teachers, colleagues, and students who have influenced our approach to the science and practice of endocrinology and metabolism. Foremost among these are Drs. John Eagar Howard and Kenneth L. Zierler of Johns Hopkins Medical Center, Baltimore, Maryland; Francis P. Muldowney of University College, Dublin; the late Larry Kyle of Georgetown University Medical Center, Washington, D.C.; and Grant W. Liddle of Vanderbilt School of Medicine, Nashville, Tennessee, who brought us together for happy and productive years in the Division of Endocrinology. We are indebted to our colleagues, postdoctoral fellows, medical house

staff, and students for their stimulation and encouragement. The material in this text reflects all of these influences, and particularly the lessons diligently taught by the patients we have been privileged to treat.

The immediate preparation of this book has been aided by many. We are grateful for the helpful comments and criticisms given by those who reviewed sections during their preparation—Dr. Stanley Schwartz of Philadelphia, Drs. Rowan DeBold, Randy Linde, Brent Gooch, and Craig Sussman, all of Vanderbilt University School of Medicine, and Drs. D.K. O'Donovan, Francis P. Muldowney, Niall O'Higgins, Karina Butler, and Fergal Magee, all of Dublin. We are pleased to recognize the contributions of Mary Margaret Alsobrook Peel, who prepared many of the illustrations, and of our photographer, Dean Denis of Nashville. The special checking of references was conscientiously performed by Dana and Leora Rabin. We are happy to acknowledge the expert and enthusiastic secretarial assistance of Eileen Reid in Dublin and of Patty Adams, Bettye Ridley, Marion Gains and Pat Runsvold in Nashville. The courteous and ready assistance provided by our editors at Grune and Stratton in New York greatly eased the pressures associated with the completion of this volume.

*David Rabin, M.D.  
T. Joseph McKenna, M.D.*

# Contents

**Foreword** Grant W. Liddle, M.D. xv

**Preface** xvi

## GENERAL FEATURES OF THE ENDOCRINE SYSTEM

**Some Endocrinological Principles** 1

**Molecular Basis of Hormone Action** 2

*The Relationship between Hormones and Growth Factors. Eutopic and  
Ectopic Location of Hormones. The Hormone as Precursor to a Family  
of Neurotransmitters.*

**Coordination and Control of Endocrine Function** 5

*The Closed-loop Control Model. Intrinsic and Extrinsic Endocrine  
Rhythms. Dynamic Changes in Cellular Responses.*

**Disease States Associated with Ectopic Production of Hormones** 10

**The Clinical Approach to Endocrine Disease** 11

## THE PITUITARY GLAND

**Embryology, Functional Anatomy, and Histology of the Pituitary Gland** 13

*Anatomy of the Pituitary Gland. Hormones of the Anterior Pituitary.*

**Human Growth Hormone (HGH)** 17

*Biological Actions of Growth Hormone. GH and Growth Factors.  
GH and Substrate Metabolism.*

**Control of Growth Hormone Release** 22

*Metabolic Regulation. Regulation by Aminergic Mechanisms.  
Extrahypothalamic-Central Nervous System Control of Growth Hormone  
Release. Autoregulation of Growth Hormone Secretion. Steroid  
Modulation of Growth Hormone Secretion.*

**Syndromes of Growth Hormone Excess and Deficiency** 25

*Acromegaly and Giantism. Pituitary Giantism.*

**Isolated Growth Hormone Deficiency and Related Disorders** 33

*The Differential Diagnosis of Short Stature Treatment.*

**Prolactin: Physiology and Pathology** 43

*Actions of Prolactin. Growth and Development of the Mammary  
Gland. Summary of Breast Development and Its Hormonal Control.  
Gonadal Effects. Ontogeny of Prolactin Secretion. Control of  
Prolactin Release.*

**Prolactin Deficiency and Hyperprolactinemia** 49

*Prolactin Deficiency. Syndromes of Prolactin Excess.*



## **Adrenocorticotropin (ACTH), Thyroid-stimulating Hormone (TSH), and the Gonadotropins: States of Hypersecretion and Deficiency 54**

*Syndromes of ACTH Excess. ACTH Deficiency. Thyrotropin Hypersecretion. Thyrotropin Deficiency. Gonadotropin Excess. Gonadotropin Deficiency.*

## **An Overview of Pituitary Tumors 59**

*Symptomatology. Investigative Procedures. Differential Diagnosis. Treatment.*

## **Pituitary Apoplexy 65**

*Pathology. Symptomatology. Diagnostic Procedures. Treatment.*

## **An Overview of Hypopituitarism 66**

*Classification. Pituitary Infarction Including Sheehan's Syndrome. Other Causes of Pituitary Infarction. Other Causes of Primary Hypopituitarism. Diagnostic Procedures. Treatment.*

## **The Empty Sella Syndrome (ESS) 71**

*Classification and Etiology. Diagnostic Procedures.*

## **Craniopharyngioma 73**

*Definition and Etiology. Pathology. Symptomatology. Investigation. Treatment.*

## **Anorexia Nervosa 76**

*Clinical Characteristics. Etiology. Symptomatology. Diagnostic Procedures. Differential Diagnosis. Therapy.*

## **THE POSTERIOR PITUITARY GLAND OR THE NEUROHYPOPHYSIS**

### **Embryology, Functional Anatomy, and Histology of the Neurohypophysis 88**

*Historical Aspects. The Neurohypophysis.*

### **Basic Considerations of Water Metabolism 91**

*Water Losses in an Adult Human Being. Movement of Water in the Nephron.*

### **Biochemical Action and Control of Secretion of Arginine Vasopressin**

#### **(AVP) 93**

*Biochemical Action. Control of Secretion. Clinically Relevant Aspects of AVP Physiology.*

### **The Syndromes of Polyuria 96**

*Central Diabetes Insipidus. Primary Polydipsia. Nephrogenic Diabetes Insipidus. An Approach to the Diagnosis of Diabetes Insipidus and Related Disorders. Therapy of Patients with Diabetes Insipidus.*

### **The Hypoosmolar Syndromes 103**

*Syndromes of Hemodynamic-Related and Inappropriate Antidiuretic Hormone Secretion. Etiology and Pathogenesis. Subgroups of Inappropriate ADH Secretion. Drug-Related Inappropriate ADH Secretion. Signs and Symptoms in Experimental and Clinical SIADH.*

## **INTERMEDIARY METABOLISM AND THE SYNDROMES OF DIABETES MELLITUS**

### **Some Considerations on Intermediary Metabolism of Carbohydrate, Lipid, and Protein 111**

*Carbohydrate. Lipid. Protein.*

### **Biologic Effects of Insulin and Glucagon 120**

*Biochemical Actions of Insulin and Glucagon. Physiological Roles of Insulin and Glucagon.*

<b>Fuel Flux in Intact Man</b>	<b>125</b>
<b>Events Associated with Prolonged Starvation and with Substrate Excess</b>	<b>128</b>
<b>Islets of Langerhans</b>	<b>131</b>
<i>Insulin: Biosynthesis and Control.</i>	<i>Glucagon: Biosynthesis and Control.</i>
<b>Diabetes Mellitus: Definition and Modern Diagnostic Criteria</b>	<b>138</b>
<b>Characterization of the Different Types of Diabetes Mellitus</b>	<b>142</b>
<i>Type I Insulin-Dependent Diabetes Mellitus (Juvenile Onset Diabetes).</i>	
<i>Type II Noninsulin-Dependent Diabetes Mellitus.</i>	
<b>The Treatment of Diabetes Mellitus</b>	<b>149</b>
<i>General Principles.</i>	<i>Dietary Regimens.</i>
<i>Mellitus.</i>	<i>The Use of Insulin in Diabetes Mellitus.</i>
<b>Problems of Insulin Therapy</b>	<b>154</b>
<i>Insulin Allergy.</i>	<i>Insulin Resistance.</i>
<i>Injection.</i>	<i>Local Fat Changes at the Site of</i>
<i>Insulin Hypoglycemia.</i>	
<b>The Oral Hypoglycemic Agents</b>	<b>158</b>
<i>Phenformin.</i>	
<b>Hemoglobin A1c</b>	<b>160</b>
<b>Acute Failure of Diabetic Control: The Syndromes of Ketoacidosis, Hyperosmolar Hyperglycemia, and Lactic Acidosis</b>	<b>161</b>
<i>Diabetic Ketoacidosis.</i>	<i>Hyperosmolar Hyperglycemic Diabetic Coma</i>
<i>(HHDC).</i>	<i>Lactic Acidosis.</i>
<b>Microangiopathy and Macroangiopathy</b>	<b>178</b>
<b>The Diabetic Neuropathies</b>	<b>179</b>
<i>Functional Anatomy.</i>	<i>Diabetic Neuropathy: Morphology and</i>
<i>Pathogenesis.</i>	<i>Clinical Features of Diabetic Neuropathies.</i>
	<i>Therapy.</i>
<b>Diabetic Retinopathy</b>	<b>188</b>
<i>Classification.</i>	<i>Evolution of Diabetic Retinopathy.</i>
<i>Rubeosis Iridis Diabetica.</i>	<i>Therapy.</i>
<b>Diabetic Nephropathy</b>	<b>194</b>
<i>Anatomy of the Normal Glomerulus in Man.</i>	<i>Pathology in Diabetes Mellitus.</i>
<i>Clinical Manifestations of the Diabetic Nephropathies.</i>	
<i>Therapy.</i>	
<b>The Diabetic Foot</b>	<b>197</b>
<i>Pathology and Clinical Presentation.</i>	<i>Therapy.</i>
<b>Surgery in the Diabetic</b>	<b>199</b>
<b>Diabetes Mellitus in Pregnancy</b>	<b>199</b>
<i>Metabolic Changes in Pregnancy.</i>	<i>Therapeutic Goals for the Pregnant</i>
<i>Diabetic.</i>	<i>Problems in the Diabetic Pregnancy.</i>

## THE HYPOGLYCEMIAS

<b>Maintenance of Glucose Homeostasis</b>	<b>210</b>
<b>Clinical Presentation of Hypoglycemia</b>	<b>210</b>
<b>Classification and Etiology of Hypoglycemia</b>	<b>211</b>
<i>Postprandial Hypoglycemic Syndromes.</i>	<i>Postabsorptive Hypoglycemic</i>
<i>Syndromes.</i>	<i>Induced Hypoglycemia.</i>
<i>Treatment.</i>	<i>Investigative Schedule and</i>



**OTHER RARE PANCREATIC ISLET CELL SYNDROMES****The Glucagonoma Syndrome 224****The Somatostatinoma Syndrome 225***Somatostatinoma.***The Watery Diarrhea-Hypokalemia-Achlorhydria Syndrome 227***The Watery Diarrhea-Hypokalemia-Achlorhydria (WDHA) Syndrome or  
Pancreatic Cholera. Differential Diagnosis Including a Note on  
Gastrinoma.***OBESITY****Definition of Obesity 230****Normal Control of Adipose Tissue Stores 230****Etiological Factors in Obesity 231****Management of Obesity 233***Conservative Regimens. Drug Therapy of Obesity. Surgical Therapy  
in the Treatment of Morbid Obesity.***DISORDERS OF LIPID METABOLISM****Definition and Classification of Hyperlipoproteinemia 242****Structure and Function of Lipoproteins 242***Normal Lipid Transport.***Disorders of Lipid Transport 247***Disorders of Triglyceride Metabolism. Hyperlipoproteinemia Due to  
Enhanced Peripheral Levels of Intermediate-Density Lipoproteins.  
Disorders of Cholesterol Accumulation. Combined Hypertriglyceridemia  
and Hypercholesterolemia. Disorders Associated with Low Levels of  
Circulating Lipids.***Guidelines in Therapy of Hyperlipoproteinemia 251****Lipid Disorders and Diabetes Mellitus 252****THE THYROID****Anatomy and Physiology of the Thyroid 254***Thyroid Anatomy. Thyroid Physiology.***Examination of the Thyroid 263****Thyrotoxicosis 263***Definition. Etiology and Classification of Hyperthyroidism.  
Pathology. Symptomatology. Differential Diagnosis.  
Investigation. Diagnostic Problems. Investigative Schedule.  
Treatment of Thyrotoxicosis and Thyroid Ophthalmopathy. Treatment  
Problems. Prognosis.***Hypothyroidism 289***Definition. Classification. Etiology. Pathology.  
Symptomatology. Differential Diagnosis. Investigative  
Procedures. Investigative Schedule. Diagnostic Problems.  
Treatment. Treatment Problems. Complications. Prognosis.***Thyroiditis 303***Acute (Suppurative) Thyroiditis. Subacute Thyroiditis. Chronic  
Thyroiditis. Riedel's Struma.*

**Euthyroid Goiter 312**

Definition. Etiology. Pathology. Symptomatology. Differential  
 Diagnosis. Diagnostic Procedures. Investigative Schedule.  
 Diagnostic Problems. Treatment. Treatment Problems.  
 Complications. Prognosis.

**Thyroid Nodules and Thyroid Cancer 315**

Definition. Classification. Etiology. Pathology. Incidence.  
 Symptomatology. Differential Diagnosis. Diagnostic Procedures.  
 Investigative Schedule. Diagnostic Problems. Management.  
 Management Problems. Complications. Prognosis.

**MINERAL METABOLISM AND ITS DISORDERS****Calcium and Phosphate Homeostasis 324****Physiology 324**

Parathyroid Hormone. Vitamin D. Calcitonin.

**Disorders of Calcium Homeostasis 329****Hypercalcemia 329****Hyperparathyroidism 329**

Definition. Classification and Etiology. Pathology. Symptoms and  
 Signs. Investigation of Hypercalcemia. Localization of PTH  
 Source. Differential Diagnosis of Hyperparathyroidism  
 (Hypercalcemia). Investigative Schedule. Diagnostic Problems.  
 Treatment. Problems in Management.

**Secondary and Tertiary Hyperparathyroidism 354****Hypocalcemia 354****Hypoparathyroidism and Pseudohypoparathyroidism 355**

Definition. Etiology and Classification. Symptomatology.  
 Diagnosis. Investigative Schedule. Problems in Diagnosis.  
 Treatment. Complications and Prognosis.

**Hypomagnesemia 361****Vitamin D Deficiency 362****Renal Failure 364****Neonatal Hypocalcemia 364****Increased Bone Avidity for Calcium 364****Acute Pancreatitis 364****Miscellaneous Causes of Hypocalcemia 364****Renal Stone Disease 371**

Incidence. Pathogenesis of Nephrolithiasis.

**Idiopathic Nephrolithiasis (Hypercalciuria) 374**

Definition. Etiology. Classification. Pathology.  
 Symptomatology. Differential Diagnosis. Investigative  
 Procedures. Investigative Schedule. Diagnostic Problems.  
 Treatment. Choice of Treatment.

**Urinary Tract Stones Associated with Infection—Struvite Stone Disease 383****Uric Acid Stones 384****Cystinuria 384****Hyperoxaluria 385****Bone Metabolism 387**

Physiology.

**Metabolic Bone Disease: 392****Osteomalacia 392**

Definition. Etiology. Pathology. Symptomatology of Rickets and  
 Osteomalacia. Differential Diagnosis. Investigative Procedures.  
 Investigative Schedule. Problems in Diagnosis. Treatment and  
 Treatment Problems. Complications and Prognosis.



<b>Osteoporosis</b>	<b>403</b>
Definition. Etiology. Pathology. Clinical Presentation.	
Differential Diagnosis. Investigative Procedures. Investigative	
Schedule. Problems in Diagnosis. Treatment. Treatment	
Problems. Complications and Prognosis.	
<b>Renal Osteodystrophy</b>	<b>414</b>
Definition. Etiology. Pathology. Symptomatology. Differential	
Diagnosis. Diagnostic Procedures. Treatment. Treatment	
Problems. Complications and Prognosis.	
<b>Paget's Disease (Osteitis Deformans)</b>	<b>421</b>
Definition. Etiology. Pathology. Clinical Presentation.	
Differential Diagnosis. Diagnostic Procedures. Treatment.	

## ADRENAL CORTEX

<b>The Adrenal Glands and Glucocorticoid Physiology</b>	<b>430</b>
Anatomy. Glucocorticoids.	
<b>Cushing's Syndrome</b>	<b>434</b>
Definition. Etiology and Classification. Pathology.	
Symptomatology. Differential Diagnosis. Investigations.	
Diagnostic Difficulties. Investigative Schedule. Treatment: Cushing's	
Disease. Treatment Problems: Cushing's Disease. Treatment: Adrenal	
Tumor. Treatment: Ectopic ACTH Production. Prognosis.	
<b>Adrenal Insufficiency</b>	<b>454</b>
Definition. Classification. Etiology and Pathology.	
Symptomatology. Differential Diagnosis. Diagnostic Procedures.	
Problems in Diagnosis. Investigative Schedule. Treatment.	
Treatment Problems. Complications and Prognosis.	
<b>Aldosterone Physiology, Excess, and Depletion</b>	<b>466</b>
Physiological Control of Aldosterone Secretion.	
<b>Aldosteronism</b>	<b>469</b>
Definition. Classification.	
<b>Primary Aldosteronism</b>	<b>469</b>
Etiology. Pathology. Symptomatology. Differential Diagnosis.	
Diagnostic Procedures. Diagnostic Difficulties. Investigative	
Schedule. Treatment. Treatment Problems. Prognosis.	
<b>Secondary Aldosteronism</b>	<b>474</b>
<b>Aldosterone Deficiency</b>	<b>475</b>
Hyporeninemic Hypoaldosteronism. Congenital Enzymatic Defects in	
Aldosterone Biosynthesis. Pseudohypoaldosteronism. Treatment.	
<b>Adrenal Sex Hormones: Physiology and Pathology</b>	<b>479</b>
Physiological Considerations. Pathological Considerations.	
<b>Congenital Adrenal Hyperplasia</b>	<b>480</b>
21-Hydroxylase Deficiency. 3 $\beta$ -ol-Dehydrogenase, $\Delta^{4-5}$ -Isomerase	
Enzyme Deficiency. 11 $\lambda$ -Hydroxylase Deficiency. 17 $\alpha$ -Hydroxylase	
Deficiency. Lipoid Adrenal Hyperplasia	
<b>Idiopathic Hirsutism</b>	<b>491</b>
<b>Androgen-Secreting Adrenal Tumors</b>	<b>497</b>
<b>Estrogen-Secreting Adrenal Tumors</b>	<b>497</b>

## THE SYMPATHETIC NERVOUS SYSTEM, CATECHOLAMINES, AND THE ADRENAL MEDULLA 501

Organization of the Sympathoadrenal System. Embryology.
Biosynthesis of Catecholamines. Inactivation of Catecholamines.

*Adrenergic Receptors. Physiology of the Sympatheticoadrenal System. Pheochromocytoma. Disorders Characterized by Underactivity of the Sympathetic Adrenal System.*

## THE OVARY

### Functional Anatomy and Histology of the Ovary 516

*Embryology. Dynamic Changes in Ovarian Follicle.*

### Gonadotropins of Pituitary Origin: FSH and LH 520

*Chemistry of the Pituitary Gonadotropins. The Pituitary Gonadotroph. The Ontogeny of Gonadotropin Secretion. Control of Gonadotropin Release. Landmarks at Puberty.*

### The Menstrual Cycle 525

*Sequences of Events During the Menstrual Cycle. Ovulation. The Luteal Phase.*

### Biochemical Actions of the Gonadotropins 528

### The Syndromes of Amenorrhea 528

*The Development of the Internal and External Genitalia. Definition and Classification.*

### Absence of Uterus Including Syndromes of Male Pseudohermaphroditism 530

*Amenorrhea Due to Anatomical Defects of the Outflow Tract. XY Genotype—The Syndromes of Male Pseudohermaphroditism.*

### Amenorrhea, Presence of a Uterus: Ovarian Failure 539

*Gonadal Dysgenesis and Related Disorders.*

### Gonadotropin Deficiency 543

*Isolated Deficiency of FSH.*

### Functional Hypothalamic Amenorrhea 549

*Low Gonadotropin Syndromes with Euprolactinemia. Classification. Etiologic Considerations.*

### Polycystic Ovarian Disease 552

### Diagnostic Considerations in Amenorrhea 555

### An Approach to the Investigation and Treatment of Infertility 557

*Genital Pathology. Anovulation.*

### Sexual Precocity 561

*Differential Diagnosis. Treatment.*

### Ovarian Tumors 563

*The Feminizing Mesenchymoma. The Sertoli-Leydig-Cell Tumors. Leydig-Cell Tumors. Lipid-Cell Tumors. The Luteoma of Pregnancy.*

## THE TESTIS

### Embryology and Anatomy of the Testis 571

*Embryology. Anatomy of the Testis.*

### The Physiology of Puberty 574

### The Regulation of Gonadotropin Secretion in Males 577

*Steroid Influences on Gonadotropin Secretion. Gonadotropin Actions on the Testis.*

### Primary Testicular Disorders 578

*Testicular Disease Associated with Chromosomal Abnormalities. Dysgenetic Male Pseudohermaphroditism. Nonchromosomal Abnormalities of the Male Gonad.*



**Hypogonadotropic Hypogonadism: Gonadotropin Deficiency. 590**

*Etiology. Pathology. Symptomatology. Investigation.*  
*Differential Diagnosis. Secondary Postpubertal Gonadotropin*  
*Insufficiency.*

**Varicocele 595**

*Definition and Etiology. Clinical Features. Investigation.*  
*Treatment.*

**Cryptorchidism 596**

*Definition and Etiology. Differential Diagnosis. Symptomatology.*  
*Pathology. Treatment.*

**An Approach to the Evaluation and Therapy of Male Infertility 598**

*Sexual Dysfunction. Investigative Schedule After Exclusion of Sexual*  
*Dysfunction.*

**Precocious Sexual Maturation 602**

*Definition and Classification. Etiology. Differential Diagnosis of*  
*Precocious Sexual Maturation. Treatment.*

**Gynecomastia 604**

*Definition and Pathology. Etiology. Diagnosis and Treatment.*

**Testicular Tumors 607**

*Pathology. Symptomatology. Diagnosis. Differential*  
*Diagnosis. Treatment.*

**POLYENDOCRINE SYNDROMES AND PARAENDOCRINE DISEASES**

*Polyendocrine Syndromes: Definition.*

**Multiple Endocrine Neoplasia Syndromes 614**

*Classification. Etiology.*

**Multiple Endocrine Neoplasia Type I 616**

*Pathology. Symptomatology. Differential Diagnosis. Diagnostic*  
*Procedures. Investigational Problems. Treatment.*

**Multiple Endocrine Neoplasia Type II 619**

*Pathology. Symptomatology. Differential Diagnosis.*  
*Investigational and Screening Procedures. Diagnostic Problems.*  
*Treatment. Treatment Problems. Complications and Prognosis.*

**Autoimmune Pluriglandular Syndrome 625**

*Definition. Etiology. Pathology. Symptomatology. Differential*  
*Diagnosis. Diagnostic Procedures. Diagnostic Difficulties.*  
*Treatment. Prognosis.*

**Carcinoid Syndromes 627**

*Classical Carcinoid Syndrome. Foregut Carcinoid Tumors. Diagnosis*  
*and Therapy.*

**Mastocytosis 629**

*The Mast Cell. The Clinical Manifestations of Mastocytosis.*  
*Diagnosis. Differential Diagnosis. Therapy.*

**Index 633**

# GENERAL FEATURES OF THE ENDOCRINE SYSTEM

## Some Endocrinological Principles

The endocrine system includes all groups of cells that secrete directly into the bloodstream and lymphatics and is in contrast to exocrine glands such as the gall bladder, the mammary and salivary glands whose secretions are conducted along ducts. Hormones are the physiologically active products of endocrine glands. The endocrine system has traditionally included a series of well-defined glands: the hypophysis, thyroid, parathyroids, adrenals, pancreatic islets, ovaries, and testes. It is clearly established, however, that many organs not classically considered to be endocrine glands contain groups of cells that synthesize hormones and under certain conditions secrete these into the bloodstream. Later in this chapter, "eutopic" and "ectopic" production of hormones will be further considered.

The vascular and lymphatic systems are the common channels whereby hormones influence metabolic processes. The output of the endocrine system is, for the most part, not confined by internal anatomic boundaries, but gains access to and potentially can influence most organs, tissues, and cells; hence, Fuller Albright's statement that endocrinology is an indivisible division of internal medicine.<sup>1</sup> An essential prerequisite for responsiveness of a cell to a hormone is the presence of a specific receptor for the hormone, either on the cell surface or within the cytoplasm of the cell. Hormones fall into two main classes: (1) steroids and thyronines, which are lipid soluble; and (2) polypeptides and catecholamines, which are water soluble. Steroid hormones are produced by endocrine glands of mesodermal origin (the adrenal cortex and the gonads), whereas polypeptides, catecholamines, and thyronines are secreted by glands of ectodermal or neuroectodermal origin. Hormones circulate in extremely small concentrations; for example, insulin and human growth hormone are present in blood in concentrations of only a few nanograms (ng)/ml of plasma. That is of the order of  $10^{-11}M$ . Metabolic effects can be produced by as little as  $10^{-8}M$  of insulin per gram of muscle or adipose tissue in vivo.

The ability of the cell to select out a particular hormone circulating in such low concentration is dependent upon the presence of specific *receptors* for the hormone, either on the cell surface or within the cytoplasm. The receptor thus serves as a means of recognition between the cell and a circulating

hormone. The dynamic role of receptors in modulating the action of hormones will be discussed later. For the present, consider the hypothetical cell shown in Figure 1. The cell can take up various substances from, and release the same or other substances into, its immediate environment. Uptake and release are highly specific and are dependent upon the presence of specific carriers (for example, for sugar transport) and may require the expenditure of energy by the cell, that is the use of adenosine 5'-triphosphate (ATP). The cell has or can synthesize the enzymatic machinery to dissimilate materials along various pathways. These may be either catabolic, such as the combustion of carbohydrate or fat to carbon dioxide and water, or anabolic, such as the incorporation of amino acid into protein. It has long been an endocrine axiom that hormones do not initiate metabolic processes within the cell, but do alter their rates of reaction.

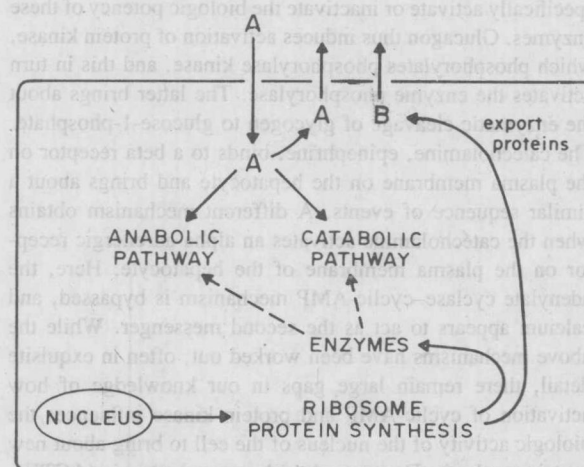


Fig. 1. Schematic representation of the cell and some of its important activities. Substances are taken up by the cell and may subsequently undergo conversion via either catabolic or anabolic pathways. Enzymes, catalyzing these pathways, are synthesized in the cell directed by the nucleus. The cell may export substances, which it itself has synthesized, or it may release substances, which it has previously taken up from its environment.

# Molecular Basis of Hormone Action

Hormones influence cellular metabolic processes either directly or indirectly, for example, by promoting the synthesis of one or a family of growth factors. As a generalization, the combination of a hormone with its receptor brings about changes within the cell by one of two mechanisms: (1) the generation of a second messenger within the cell; or (2) the translocation of the hormone-receptor complex into the nucleus, where the complex initiates changes within the chromatin, resulting in production of messenger RNA, and in turn initiating new protein synthesis by the cell. In general, polypeptide hormones and catecholamines appear to act via the former mechanism following interaction of hormone with its receptor at the cell surface. Steroids in the main are freely permeable to the cell membrane and exert their effects via the second mechanism.

Certain principles of the so-called "second messenger hypothesis" will now be examined more closely. As an example, turn to the interaction of glucagon with the liver cell membrane (Fig. 1). Specific binding of glucagon to its receptor is coupled with the activation of a membrane-bound enzyme, adenylate cyclase. This coupling mechanism is complex and requires the interaction of guanosine 5'-triphosphate (GTP) and other macromolecules. Activation of adenylate cyclase brings about the catalysis of ATP to adenosine 3':5'-cyclic phosphate (cyclic-AMP). The latter binds to the regulatory subunit of protein kinase, thereby liberating the catalytic subunit of this enzyme. This in turn initiates the phosphorylation of certain key enzymes that, *pari passu*, either specifically activate or inactivate the biologic potency of these enzymes. Glucagon thus induces activation of protein kinase, which phosphorylates phosphorylase kinase, and this in turn activates the enzyme phosphorylase. The latter brings about the enzymatic cleavage of glycogen to glucose-1-phosphate. The catecholamine, epinephrine, binds to a beta receptor on the plasma membrane of the hepatocyte and brings about a similar sequence of events. A different mechanism obtains when the catecholamine activates an alpha-adrenergic receptor on the plasma membrane of the hepatocyte. Here, the adenylate cyclase-cyclic-AMP mechanism is bypassed, and calcium appears to act as the second messenger. While the above mechanisms have been worked out, often in exquisite detail, there remain large gaps in our knowledge of how activation of cyclic-AMP and protein kinase influences the biologic activity of the nucleus of the cell to bring about new protein synthesis. For example, adrenocorticotropin (ACTH), acting on the adrenal, and luteinizing hormone (LH), acting on the Leydig cell, initiate an increase in steroidogenesis associated with the activation of one or several enzymes of the steroidogenic pathway. The intermediary steps whereby cyclic-AMP brings about an increase in 20,22-cholesterol-lyase activity remain unclear. Similarly, cyclic-AMP initiates an increase in human chorionic gonadotropin (HCG) synthesis by trophoblastic tumor cell lines, a process which involves the mediation of the nucleus and new protein synthesis. Again, the detailed biochemical steps whereby this process

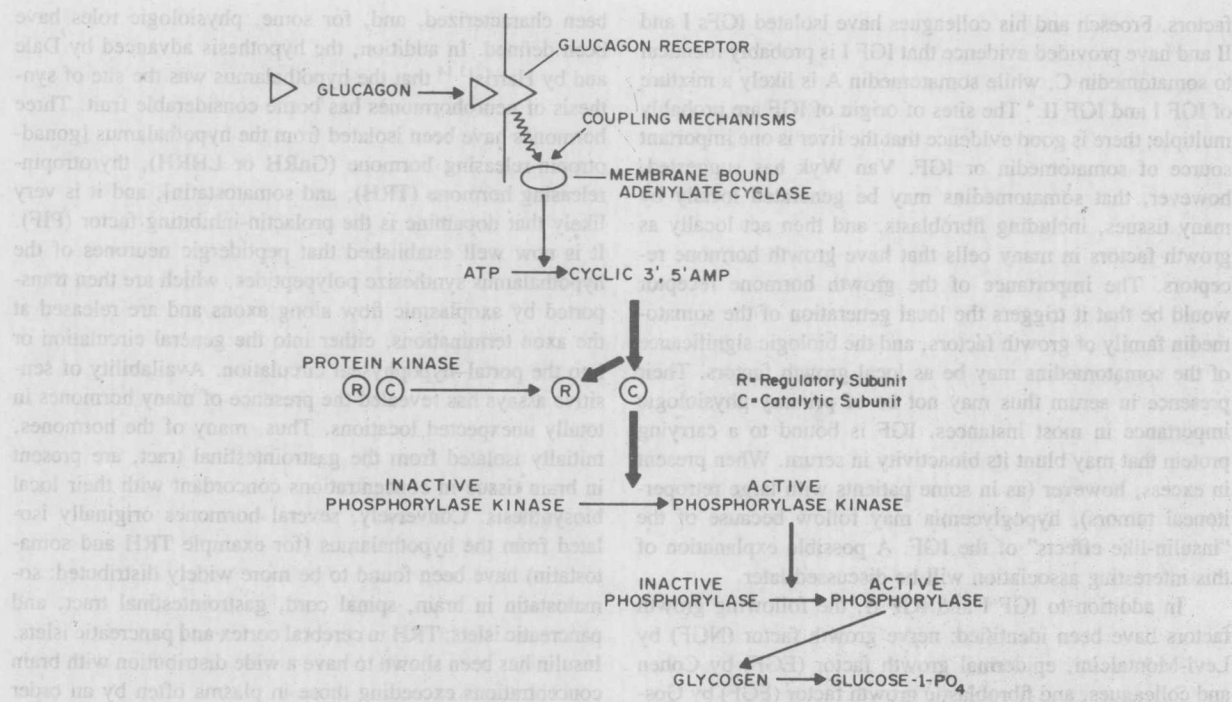
is accomplished remain obscure. It is believed that insulin and prolactin also act via production of second messengers by the cell. Prolactin binds to a specific receptor and brings about an increase in protein kinase without a concomitant activation of adenylate cyclase. The putative second messenger for insulin has eluded identification, but, at the time of writing, several laboratories appear to agree that it is a small polypeptide fragment cleaved off the cell membrane following interaction of insulin and its receptor. This second messenger may be responsible for both the membrane and the intracellular metabolic effects of insulin. Kono has suggested that the insulin second messenger brings about translocation of a carrier from an intracellular locus to the cell membrane.<sup>2</sup> This leads to profound changes in the properties of the cell membrane (e.g., enhancement of D-glucose transport) and dramatic changes in the flux of certain ions, such as potassium. The putative second messenger of insulin thus has diverse effects, which are cumulatively anabolic, on the intermediary metabolism of the cell.

Steroid-mediated changes in cell physiology are brought about in general by interaction between the hormone and its receptor, which is located in the cytosol (Fig. 2). The hormone-receptor complex is then translocated to the nucleus where it binds specifically to a locus on the chromatin, activating RNA polymerase, with ultimate synthesis of one or several specific messenger RNAs. These products leave the nucleus and travel to the ribosome where they direct the synthesis of one or a family of proteins. The ability of the steroid to activate the genome thus permits the appearance of specific gene products, which are either utilized intracellularly or which may be exported. Two characteristics of this mode of hormone action are: (1) a delay in the generation of the hormonal effects; and (2) inhibition of hormonal action by agents (such as actinomycin) that block DNA-directed RNA synthesis.

## THE RELATIONSHIP BETWEEN HORMONES AND GROWTH FACTORS

In addition to what are classically referred to as hormones, whose sites of synthesis are recognized, there have been identified an increasing number of so-called "growth factors." Certain growth factors were initially recognized in serum, and some are clearly dependent for adequate synthesis on the presence of a trophic hormone. Take as an example the insulin-like growth factors (IGF) I and II, whose structures have been determined, and trace their history. The resolution of this problem has its genesis in two apparently discrete sets of findings: first, the presence in plasma of biologic activity resembling that of insulin, but which could not be suppressed by addition of anti-insulin antiserum. Methods were evolved for the extraction of so-called "soluble nonsuppressible insulin-like activity" (NSILA) by Froesch, Humble, and their colleagues.<sup>3</sup> Concurrently, it was recognized that the powerful effects of growth hormone observed *in vivo* were absent under *in vitro* conditions. The second set of findings commenced

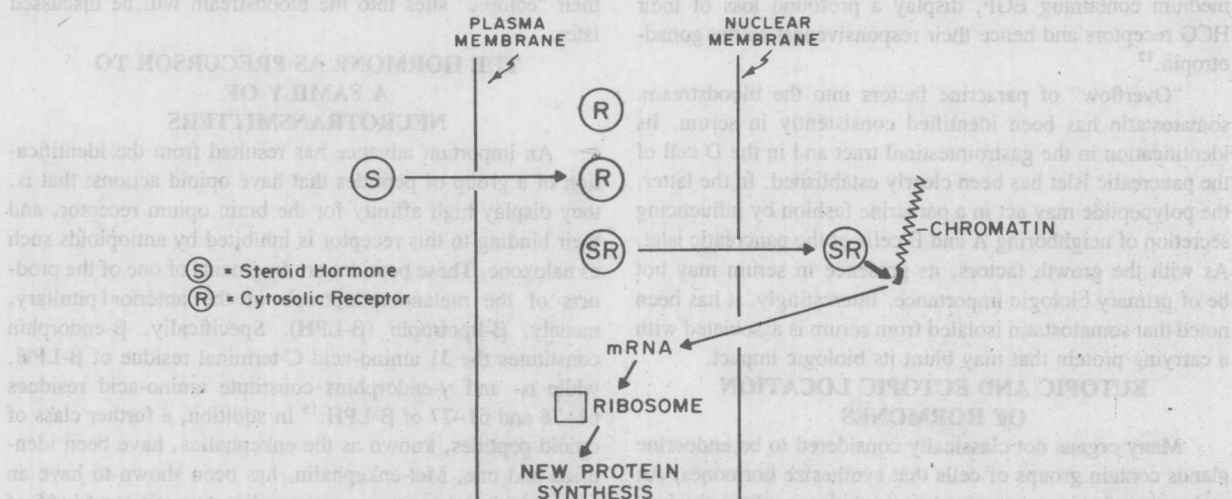




**Fig. 1.** Schematic representation of the action of the polypeptide hormone, glucagon. Glucagon interacts with a specific receptor on the cell membrane, and this is coupled to the adenylate cyclase system. Activation of the latter results in the production of cyclic-AMP, which in turn stimulates protein kinase. The latter results in the phosphorylation of a series of enzymes, culminating in the activation of phosphorylase, which catalyzes the conversion of glycogen to glucose-1-phosphate.

with the classical studies by Salmon and Daughaday.<sup>4</sup> They established that injection of the growth hormone into experimental animals was followed by the appearance in serum of a substance that increased the incorporation of radioactive sulfate into mucopolysaccharide-protein complexes of rat cartilage. Hall et al.<sup>5</sup> and Van Wyk et al.<sup>6</sup> developed methods for extraction of the so-called "sulfation factor" (SF) from

plasma. It became apparent that the SF, now renamed "somatomedin" and subdivided into A, B, and C fractions, possessed insulin-like activity under in vitro conditions and furthermore could compete for binding to the insulin receptor in several in vitro membrane systems. Purification of NSILA and somatomedin C was followed by the generation of antibodies and the development of radioimmunoassays for these



**Fig. 2.** Schematic representation of the interaction of a steroid hormone with the cell. The steroid hormone enters the cytoplasm of the cell where it interacts with a specific receptor. The steroid-receptor complex is then translocated to the nucleus where it results in the activation of messenger RNA, which exits the nucleus and initiates new protein synthesis in the cytosol.

factors. Froesch and his colleagues have isolated IGFs I and II and have provided evidence that IGF I is probably identical to somatomedin C, while somatomedin A is likely a mixture of IGF I and IGF II.<sup>4</sup> The sites of origin of IGF are probably multiple; there is good evidence that the liver is one important source of somatomedin or IGF. Van Wyk has suggested, however, that somatomedins may be generated locally by many tissues, including fibroblasts, and then act locally as growth factors in many cells that have growth hormone receptors. The importance of the growth hormone receptor would be that it triggers the local generation of the somatomedin family of growth factors, and the biologic significance of the somatomedins may be as local growth factors. Their presence in serum thus may not be of primary physiologic importance in most instances. IGF is bound to a carrying protein that may blunt its bioactivity in serum. When present in excess, however (as in some patients with large retroperitoneal tumors), hypoglycemia may follow because of the "insulin-like effects" of the IGF. A possible explanation of this interesting association will be discussed later.

In addition to IGF I and IGF II, the following growth factors have been identified: nerve growth factor (NGF) by Levi-Montalcini, epidermal growth factor (EGF) by Cohen and colleagues, and fibroblastic growth factor (FGF) by Gospodarowicz.<sup>7-9</sup> These are the forerunners of a family of growth factors that exert trophic influences primarily on one set of tissues, but often have far wider biologic effects. For example, EGF exerts important trophic influences on the epidermis, including the cornea. Epidermal growth factor also enhances the rate of growth of fibroblasts in culture, however, and elucidation of its mechanism of action may shed light on fundamental factors involved in cell differentiation and growth. The placenta is rich in EGF receptors, and EGF has been shown to enhance synthesis and release of both HCG and progesterone from a trophoblastic tumor cell line.<sup>10,11</sup> In addition, Ascoli has made the important observation that Leydig cells derived from a mouse tumor, when grown in culture medium containing EGF, display a profound loss of their HCG receptors and hence their responsiveness to the gonadotropin.<sup>12</sup>

"Overflow" of paracrine factors into the bloodstream: somatostatin has been identified consistently in serum. Its identification in the gastrointestinal tract and in the D cell of the pancreatic islet has been clearly established. In the latter, the polypeptide may act in a paracrine fashion by influencing secretion of neighboring A and B cells of the pancreatic islet. As with the growth factors, its presence in serum may not be of primary biologic importance. Interestingly, it has been noted that somatostatin isolated from serum is associated with a carrying protein that may blunt its biologic impact.

#### EUTOPIC AND ECTOPIC LOCATION OF HORMONES

Many organs not classically considered to be endocrine glands contain groups of cells that synthesize hormones. An early example was recognized in the kidney, where the juxtaglomerular apparatus actively synthesizes the enzyme, renin, which it secretes into the renal-venous bloodstream. During the last decade, the gastrointestinal tract has emerged as the source of numerous hormones. Many of these have

been characterized, and, for some, physiologic roles have been defined. In addition, the hypothesis advanced by Dale and by Harris<sup>13,14</sup> that the hypothalamus was the site of synthesis of neurohormones has borne considerable fruit. Three hormones have been isolated from the hypothalamus [gonadotropin-releasing hormone (GnRH or LHRH), thyrotropin-releasing hormone (TRH), and somatostatin], and it is very likely that dopamine is the prolactin-inhibiting factor (PIF). It is now well established that peptidergic neurones of the hypothalamus synthesize polypeptides, which are then transported by axoplasmic flow along axons and are released at the axon terminations, either into the general circulation or into the portal-hypophyseal circulation. Availability of sensitive assays has revealed the presence of many hormones in totally unexpected locations. Thus, many of the hormones, initially isolated from the gastrointestinal tract, are present in brain tissue in concentrations concordant with their local biosynthesis. Conversely, several hormones originally isolated from the hypothalamus (for example TRH and somatostatin) have been found to be more widely distributed: somatostatin in brain, spinal cord, gastrointestinal tract, and pancreatic islets; TRH in cerebral cortex and pancreatic islets. Insulin has been shown to have a wide distribution with brain concentrations exceeding those in plasma often by an order of magnitude or greater. The role of hormones in the brain in what would traditionally be termed "ectopic loci" remains to be defined. An attractive hypothesis is their utilization as neurotransmitters. Human chorionic gonadotropin has traditionally been considered to be a unique product of the trophoblast. It has now been identified in most normal tissues, including the testis, pancreas, and gastrointestinal tract. The presence of hormones in diverse locations complicates a previously clear designation of hormones as either eutopic or ectopic. Of importance is that the presence of the hormone, e.g., insulin or HCG, inside a cell is not necessarily associated with its export from the cell into the peripheral circulation.

The consequences of secretion of these hormones from their "ectopic" sites into the bloodstream will be discussed later.

#### THE HORMONE AS PRECURSOR TO A FAMILY OF NEUROTRANSMITTERS

An important advance has resulted from the identification of a group of peptides that have opioid actions; that is, they display high affinity for the brain opium receptor, and their binding to this receptor is inhibited by antiopioids such as naloxone. These peptides are fragments of one of the products of the melanocorticotroph of the anterior pituitary, namely,  $\beta$ -lipotropin ( $\beta$ -LPH). Specifically,  $\beta$ -endorphin constitutes the 31 amino-acid C-terminal residue of  $\beta$ -LPH, while  $\alpha$ - and  $\gamma$ -endorphins constitute amino-acid residues 61-76 and 61-77 of  $\beta$ -LPH.<sup>15</sup> In addition, a further class of opioid peptides, known as the enkephalins, have been identified and one, Met-enkephalin, has been shown to have an amino-acid composition corresponding to positions 61-65 of  $\beta$ -LPH. It is possible that these opioid-like peptides may derive from the cleavage of  $\beta$ -LPH, and/or they may be synthesized de novo in the hypothalamus, in the brain, and in posterior horn cells of the spinal cord.